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# Use of Proton Pump Inhibitors and Risk of Pancreatic Cancer: A Nationwide Case-Control Study Based on the French National Health Data System (SNDS)

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1 **TITLE PAGE**

2 **Title:** Use of Proton Pump Inhibitors and Risk of Pancreatic Cancer: A Nationwide Case-  
3 Control Study Based on the French National Health Data System (SNDS)

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16 **Running Title:** Use of Proton Pump Inhibitors and Risk of Pancreatic Cancer

17 **Abbreviations:** H2RA, Histamine-2-Receptor Antagonist; OTC, over-the-counter; PPI,  
18 Proton Pump Inhibitor; SNDS, French National Health Data System

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30 the final manuscript.

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33

34 **ABSTRACT**

35 **Background:** Only a few studies investigated the association between proton pump  
36 inhibitors (PPIs) use and pancreatic cancer, with inconsistent results. Moreover, these  
37 studies had a number of methodological limitations. Our objective was to assess this  
38 association in a nationwide case-control study.

39 **Methods:** We used the French National Health Data System (SNDS), covering 99% of  
40 the French population since 2006. Incident cases of pancreatic cancer, identified  
41 between 2014 and 2018, were matched with up to 4 controls on year of birth, sex,  
42 frequency of hospitalization within 8 years prior to index date, and department of  
43 residence. Associations between PPIs and pancreatic cancer were estimated using  
44 conditional logistic regression models adjusted for sociodemographic characteristics,  
45 risk factors of pancreatic cancer (including diabetes mellitus, tobacco-related diseases,  
46 and morbid obesity), and other comorbidities.

47 **Results:** 23,321 cases of pancreatic cancer (mean age 69.8 years, 51.7% males) and  
48 75,937 matched controls were included. Overall, 77.8% of cases and 75.5% of controls  
49 were PPI ever users. Ever (vs. never) PPI use was associated with an increased risk of  
50 pancreatic cancer (adjusted OR [aOR]=1.05, 95% CI: 1.01-1.09). A dose-response  
51 relationship was observed (1-30 cumulative defined daily dose [cDDD]: aOR=0.92,  
52 95%CI: 0.87-0.97; 31-180 cDDD: aOR=1.05, 95%CI: 1.00-1.11; 181-1080 cDDD:  
53 aOR=1.18, 95%CI: 1.12-1.24; >1080 cDDD: aOR=1.17, 95%CI: 1.10-1.23).

54 **Conclusions:** Based on these findings, a slight increase in the risk of pancreatic cancer  
55 associated with high cumulative doses of PPIs cannot be excluded.

56 **Impact:** Given the overuse of PPIs, efforts should be continued to limit treatments to  
57 appropriate indications and durations.

## 58 INTRODUCTION

59 Since their market introduction in the late 1980s, proton pump inhibitors (PPIs) have  
60 proven their efficacy and have become a standard treatment for acid-related conditions  
61 such as peptic ulcer disease and gastroesophageal reflux disease(1). Their use has  
62 steadily increased, and they are currently one of the most commonly prescribed classes  
63 of drug worldwide(2,3). Misuse, such as coprescribing with nonsteroidal anti-  
64 inflammatory drugs (NSAIDs) without gastrointestinal risk, or prescribing without a clear  
65 indication(3), is widespread, reaching on average 50% among outpatients(4). Despite a  
66 good overall tolerance at short-term, prolonged PPI use has raised safety concerns.  
67 Risks of long-term PPI therapy have been extensively explored in the literature, although  
68 some of them are still debated(5). Potential gastrointestinal health outcomes include  
69 infections(6), inflammatory bowel diseases(7), and malignancies(8–10). However, only a  
70 few observational studies have examined the association between PPI use and the risk  
71 of pancreatic cancer as main outcome, with inconsistent results and methodological  
72 limitations arising from limited numbers of cases or long-term PPI users, concerns of  
73 reverse causality, or inability to capture important confounders(11–18). Plausible  
74 mechanisms have been suggested for the potential carcinogenic effect of PPIs in  
75 pancreatic cancer, related to induced hypergastrinemia(19) and microbiome  
76 alterations(20). While risk factors of pancreatic cancer are still insufficiently known,  
77 incidence rates are rising in developed countries, with over 7 cases per 100,000 person-  
78 years in Northern America and Western Europe. After diagnosis, pancreatic cancer is  
79 associated with a poor prognosis, with an estimated 5-year survival rate of less than

80 5%(21–23). Thus, clarifying the impact of PPI exposure on the risk of pancreatic cancer  
81 is of major importance.

82 The aim of this study was to investigate the association between PPI use and the risk of  
83 pancreatic cancer in France, based on a large nationwide, population-based case-  
84 control study, addressing methodological limitations of previous studies.

## 85 **MATERIALS AND METHODS**

### 86 **Data Sources**

87 This study was conducted using the French National Health Data System (Système  
88 National des Données de Santé, SNDS), consisting of comprehensive  
89 sociodemographic and medical individual information for 99% of the population living in  
90 France (about 67 million people) since 2006. The database contains data about all  
91 outpatient services reimbursed by the National Health Insurance, including drugs (coded  
92 according to the Anatomical Therapeutic Chemical Classification System [ATC](24)),  
93 and physician visits. Patients with costly chronic diseases (LTD: long-term diseases),  
94 such as cancer, are fully reimbursed for their health expenditures, and the diagnosis are  
95 recorded (coded according to the International Classification of Diseases, Tenth  
96 Revision [ICD-10](25)). The database also contains diagnoses related to hospital  
97 admissions, and procedures performed during hospital stays. A detailed presentation of  
98 the SNDS databases is available in the Supplementary File S1.

### 99 **Study population**

100 *Cases*

101 We identified all patients aged 40 to 85 years, with an incident primary pancreatic cancer  
102 between January 1, 2014 and December 31, 2018. The index date was the date of first  
103 mention of pancreatic cancer (ICD-10 code C25), either as a hospital discharge  
104 diagnosis, or as a cause of long-term disease if it was further followed by a hospital  
105 discharge diagnosis within the next 3 months. We focused on pancreatic  
106 adenocarcinoma, which accounts for about 9 out of 10 of all pancreatic cancers(21,23).  
107 Thus, patients with a neuroendocrine neoplasm of the pancreas were not included. They  
108 were identified by an ICD-10 code C25.4, and/or an outpatient treatment with  
109 somatostatin analogs (ATC codes H01CB02, H01CB03) in the year following index date.  
110 To note, cases of pancreatic adenocarcinoma receiving a somatostatin analog in the  
111 perioperative setting, in order to reduce the risk of post-operative pancreatic leaks, were  
112 not excluded from the analyses.

### 113 *Controls*

114 Four controls with no diagnosis of pancreatic cancer at index date were randomly  
115 selected after matching on year of birth, sex, frequency of hospitalization within 8 years  
116 before index date (figured by the number of calendar years with at least one hospital  
117 admission, categorized as: 0, 1, 2, or  $\geq 3$ ), and department of residence. The index date  
118 of each case was assigned to the matched controls.

### 119 *Exclusion criteria*

120 Exclusion criteria for cases and controls were death on index date, absence of  
121 outpatient claim 7 or 8 years prior to index date (to assign the same length of  
122 observation to cases and to their matched controls, ensuring equal time windows to



123 measure exposure and to identify comorbidities), and history of cancer (all causes) or  
124 pancreatic abnormality within 8 years before index date (ICD-10 codes available in the  
125 Supplementary Table S1).

## 126 **Exposure to proton pump inhibitors**

127 Exposure to PPIs was defined as redeeming at least one prescription of a PPI marketed  
128 in France, namely omeprazole, esomeprazole, lansoprazole, pantoprazole, or  
129 rabeprazole (ATC codes A02BC01 to A02BC05), between January 1, 2006 and the  
130 index date. For ever users, we calculated the cumulative defined daily dose (cDDD),  
131 classified in quartile categories based on the distribution of use in cases. There is no  
132 consensus on optimal treatment duration or agreed definition of long-term PPI  
133 use(26,27). Based on information contained in the Summary of Product Characteristics  
134 (SmPC), individuals were considered long-term users if they had been exposed to a  
135 cumulative dose of 181 DDD, equivalent to a 6-month therapy within the study period.

136 The SNDS does not contain information neither on inpatient nor on over-the-counter  
137 (OTC) PPI use. However, this use accounts for a limited proportion in France. In 2015,  
138 92% of PPI boxes were delivered to outpatients and almost 97% of them were obtained  
139 from prescriptions (source: French National Agency for Medicines and Health Products  
140 Safety, ANSM).

## 141 Exclusion of incident PPI users

142 In order to allow for latency, and to minimize reverse causality, incident PPI users within  
143 2 years before index date (defined by at least one redeemed prescription of PPI within  
144 24 months prior to index date, and no redeemed prescription of PPI between 24 and 36

145 months prior to index date) were excluded from the set of cases and matched controls.  
146 Strata containing only cases or controls after exclusion of incident PPI users within 2  
147 years before index date were removed.

## 148 **Covariates**

149 Sociodemographic characteristics were affiliation to complementary universal health  
150 insurance (CMUC, free access to healthcare for low-income people under 65 years old),  
151 and social deprivation index (levels of disadvantage calculated across small geographic  
152 areas). We also identified medical covariates, defined by a diagnosis, or, if appropriate,  
153 by at least 3 redeemed prescriptions, within 8 years prior to index date (codes available  
154 in the Supplementary Table S2): (1) potential risk factors of pancreatic cancer, defined  
155 according to the current best available evidence(21,22,28,29): diabetes mellitus,  
156 tobacco-related diseases (including COPD diagnosis) or drug use, morbid obesity,  
157 alcohol-related diseases or drug use, acute pancreatitis, chronic pancreatitis, pancreatic  
158 cyst, gallstones, hepatitis B or C; (2) proxies of potential contexts of PPI treatment:  
159 gastroesophageal reflux disease, peptic ulcer, *Helicobacter pylori* eradication; (3) and  
160 other comorbidities or drug use: myocardial infarction, congestive heart failure,  
161 peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive  
162 pulmonary disease, connective tissue disease, mild liver disease, hemiplegia, moderate  
163 to severe liver disease, moderate to severe chronic kidney disease, HIV/AIDS,  
164 antihypertensive drug use, nonsteroidal anti-inflammatory drug use, statin use.

## 165 **Statistical Analysis**

166 Characteristics of the cases and matched controls were presented using descriptive  
167 statistics.

168 Associations between exposure to PPIs and pancreatic cancer were estimated based on  
169 crude and adjusted odds ratios (aOR) and their 95% confidence intervals (CIs) obtained  
170 using conditional logistic regression models. In addition to the matching variables (year  
171 of birth, sex, history of hospitalizations, and department of residence), and calendar  
172 year, accounted for by design, potential risk factors of pancreatic cancer (diabetes  
173 mellitus, tobacco-related diseases or drug use, morbid obesity, alcohol-related diseases  
174 or drugs use, acute pancreatitis, chronic pancreatitis, pancreatic cyst, gallstones,  
175 hepatitis B or C) were forced in the adjusted models. Then, final models were run  
176 introducing the remaining covariates through forward selection process.

177 Complementary analyses stratified by age group, sex, calendar year, and cancer  
178 localization were conducted. We also assessed whether the main modifiable risk factors  
179 of pancreatic cancer(28,29), which were reported with a prevalence above 1% among  
180 cases and controls, were effect modifier. To this end, we included in the model an  
181 interaction term between PPI use and the following covariates: diabetes mellitus,  
182 tobacco-related diseases or drug use, or morbid obesity.

183 The robustness of the main results was assessed in four sensitivity analyses. First, we  
184 applied a 2-year and a 4 year lag before the index date, disregarding PPI exposure in  
185 these periods, to maximize the control of reverse causality(30). Second, analyses were  
186 restricted to new PPI users, excluding patients who received a PPI in 2006. Third, we  
187 used inverse probability of treatment weighting (IPTW) to reduce confounding. Stabilized  
188 weights were computed from a logistic model using all cases and controls, adjusted for

189 all covariates (except for CMUC, only available among individuals aged under 65 years).  
190 Weights were then introduced in a logistic regression model for the outcome, including  
191 no other predictor than exposure(31–33). Fourth, a sensitivity analysis considering  
192 histamine-2-receptor antagonists (H2RAs, ATC codes A02BA01 to A02BA04) as an  
193 active comparator was conducted(34). These drugs have similar indications to PPIs, but  
194 inhibit acid secretion less profoundly than PPIs(35). Because of their well-documented  
195 superiority in relieving symptoms and healing mucosal lesions, PPIs have rapidly  
196 replaced H2RAs in treating any clinical acid-related condition(4). Most previous studies  
197 suggested a lack of association between pancreatic cancer development and H2RAs  
198 use(11,13,18). Thus, we compared the risk of pancreatic cancer between PPI and H2RA  
199 ever users, excluding those with incident PPI or H2RA use within 2 years before index  
200 date. Subjects using both PPIs and H2RAs were defined as PPI users.

201 All analyses were conducted using SAS EG (Copyright © 2017 SAS Institute Inc. Cary,  
202 NC, USA).

### 203 **Data availability**

204 The data generated in this study are not publicly available. EPIPHARE ([https://www.epi-](https://www.epi-phare.fr/en/)  
205 [phare.fr/en/](https://www.epi-phare.fr/en/)) has a regulatory permanent access to the data from the French National  
206 Health Data System (SNDS) via its constitutive bodies ANSM and CNAM. This  
207 permanent access is given according the French Decree No. 2016-1871 of December  
208 26, 2016 relating to the processing of personal data called "National Health Data  
209 System" (Décret n° 2016-1871 du 26 décembre 2016 relatif au traitement de données à  
210 caractère personnel dénommé « système national des données de santé » [Internet].  
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218 [https://www.legifrance.gouv.fr/codes/article\\_lc/LEGIARTI000037678676/](https://www.legifrance.gouv.fr/codes/article_lc/LEGIARTI000037678676/)).

219 All data were deidentified, thus, informed consent was not necessary.

## 220 **RESULTS**

221 We identified a total of 64,348 individuals aged 40-85 years, with incident pancreatic  
222 cancer between January 1, 2014 and December 31, 2018, including 58,599 (91.1%)  
223 patients with pancreatic adenocarcinoma. Among them, 37.1% (N=19,686) were  
224 excluded due to history of cancer within 8 years prior to index date. Seven cases failed  
225 to be matched with controls. Almost 30% (N=9927) of cases and 18.7% (N=24,944) of  
226 matched controls were excluded due to incident PPI use within 2 years prior to index  
227 date. Finally, the study population comprised 23,321 cases of pancreatic cancers, and  
228 75,937 matched population-controls, with a mean number of 3.3 controls per case  
229 (Figure 1).

230 The characteristics of cases and controls are shown in Table 1. Among cases, mean  
231 age at diagnosis was 69.8±10.1 years, and 51.7% were males. Compared to controls,  
232 cases had a higher prevalence of diabetes mellitus, tobacco- and alcohol-related  
233 diseases or drug use, morbid obesity, and history of acute or chronic pancreatitis. Cases

234 were also more likely to present with other comorbidities such as chronic obstructive  
235 pulmonary disease. Pancreatic cancers were most often localized to the head of the  
236 pancreas (Table 2). More than half of the cases died within one year after the index date  
237 (52.3%, N=12,202). Overall, 77.8% (N=18,141) of cases and 75.5% (N=57,307) of  
238 controls were PPI ever users, and 43.9% and 37.9% redeemed prescriptions for 181  
239 cDDD or more (Supplementary Table 3). Cases and controls were respectively exposed  
240 to  $658.3 \pm 1079.1$  and  $560.8 \pm 1009.7$  cDDD in mean during the study period. Omeprazole  
241 was the most frequently prescribed drug (in 50.8% of cases, and 47.9% of controls),  
242 followed by esomeprazole (46.0% of cases, and 40.6% of controls) (Supplementary  
243 Table S3).

244 The results of the main analysis are shown in Table 3. Ever use of PPIs was associated  
245 with a slightly increased risk of pancreatic cancer when compared to never use (crude  
246 OR=1.15, 95% CI: 1.10-1.19; aOR [final model]=1.05, 95% CI: 1.01-1.09). A dose-  
247 response relationship was observed (1-30 cDDD: aOR=0.92, 95% CI: 0.87-0.97; 31-180  
248 cDDD: aOR=1.05, 95% CI: 1.00-1.11; 181-1080 cDDD: aOR=1.18, 95% CI: 1.12-1.24;  
249 >1080 cDDD: aOR=1.17, 95% CI: 1.10-1.23). Analyses by PPI subtype showed a higher  
250 risk with esomeprazole (aOR=1.18, 95% CI: 1.14-1.22). Similar results were found when  
251 covariates included in the model were restricted to potential risk factors of pancreatic  
252 cancer only (Table 3).

253 Stratified analyses are shown in Table 4. The magnitude of the association between PPI  
254 use and risk of pancreatic cancer remained consistent across all subgroup analyses.  
255 Ever use of PPIs was associated with a significantly increased risk of pancreatic cancer  
256 among females (aOR=1.08, 95% CI: 1.02-1.15), subjects without history of diabetes

257 mellitus (aOR=1.07, 95% CI: 1.02-1.12), without history of tobacco-related disease or  
258 drug uses (aOR=1.05, 95% CI: 1.01-1.10), or without morbid obesity (aOR=1.05, 95%  
259 CI: 1.01-1.10). The associations of these risk factors with pancreatic cancer are  
260 presented in Supplementary Table S4 (history of diabetes mellitus: aOR=2.07, 95% CI:  
261 1.99-2.16; tobacco-related diseases or drug use: aOR=1.35, 95% CI: 1.28-1.42; morbid  
262 obesity: aOR=1.00, 95% CI: 0.95-1.06).

263 In sensitivity analyses, a dose-response relationship persisted after introduction of a 2-  
264 year or a 4-year lag period on PPI exposure, although the associations were of lower  
265 magnitude compared with the main analyses. Statistically significant associations were  
266 still observed, above 180 cDDD, with the 2-year-lag period (2-year lag analyses: 181-  
267 1080 cDDD: aOR=1.08, 95% CI: 1.03-1.14; >1080 cDDD: aOR=1.11, 95% CI: 1.05-  
268 1.19; 4-year lag analyses: 181-1080 cDDD: aOR=1.02, 95% CI: 0.97-1.07; >1080  
269 cDDD: aOR=1.08, 95% CI: 1.01-1.14) (Supplementary Table S5). Restriction to new PPI  
270 users (Supplementary Table S6), or IPTW approach (Supplementary Table S7)  
271 produced results consistent with those of the main analysis. We observed an increased  
272 risk of pancreatic cancer associated with PPI use compared to H2RA use, more marked  
273 at high PPI cumulative doses (181-1080 cDDD: crude OR=1.43, 95% CI: 1.06-1.92;  
274 aOR=1.15, 95% CI: 0.84-1.56; >1080 cDDD: crude OR=1.55, 95% CI: 1.15-2.08;  
275 aOR=1.15, 95% CI: 0.84-1.57) (Supplementary Table S8).

## 276 **DISCUSSION**

### 277 **Principal findings**

278 To our knowledge, the present study is the largest investigation on the risk of pancreatic  
279 cancer associated with PPI use, with 23,321 cases included. More than 3 out of 4  
280 individuals were PPI users over the study period, with a large proportion exposed to high  
281 cumulative doses (>180 cDDD). PPI use was associated with a slightly increased risk of  
282 pancreatic cancer, especially for cumulative exposure over 180 DDD. Overall, the  
283 results remained robust across subgroups, and in sensitivity analyses.

#### 284 **Comparison with the literature**

285 Three previous observational studies found no association between PPI use and  
286 pancreatic cancer (11,13,17). Limited power for analyses, or low proportion of long-term  
287 PPI users may have explained these null findings. By contrast, five studies reported  
288 increased risks, three of them conducted in Asian countries(14,16,18), while two set in  
289 European countries(12,15). However, these studies also had limitations. First, regional  
290 specificities in the distribution of pancreatic cancer risk factors or patterns of PPI use  
291 preclude generalization of their findings(14,16,18). In a study conducted in Taiwan(18),  
292 the prevalence of viral hepatitis was 10-fold higher than those observed in our study.  
293 Secondly, another study(15) found disproportionate numbers of short-term PPI users in  
294 the case group compared to the controls, leading to concerns of reverse causality.  
295 Finally, some of these studies were unable to capture major confounders such as  
296 tobacco smoking, obesity, or pancreatitis(12,15,16,18). In the present study, we sought  
297 to address such limitations through careful study design and various sensitivity analyses.  
298 We observed higher risks of pancreatic cancer among long-term PPI users, or with  
299 esomeprazole, one of the most potent PPI in decreasing gastric acidity(36). These  
300 findings were consistent with the physiopathology of PPIs described in the literature.



301 Hypergastrinemia, produced as a negative feedback of prolonged PPI use, might  
302 stimulate the overgrowth of pancreatic cells via CCK-B/gastrin like receptors. However,  
303 although exogenous administration of gastrin promotes pancreatic cancer in animal  
304 models, in humans, underlying factors are needed to reactivate CCK-B/gastrin like  
305 receptors reexpression from their postnatal silenced state to active state in cancer(37).  
306 PPI induced hypochlorhydria can also lead to major changes in the gut microbiome, with  
307 consequent potential retrograde microbe migration from the gastrointestinal tract, and  
308 modulation of the intra-tumor microbiome. There is strong evidence for the role of the  
309 gut and tumor microbiome in pancreatic cancer, that may impact pancreatic  
310 carcinogenesis, progression and resistance to therapy(20,38).

### 311 **Strengths and limitations**

312 Our study has a number of strengths. First, it was based on a nationwide database, with  
313 comprehensive sociodemographic and medical information on both outpatient and  
314 inpatient data, recorded since 2006. This allowed the inclusion of more than 23,000  
315 pancreatic cancers over a 5-year period. Second, this database is a valuable tool for  
316 detecting cancers, with expected good predictive value and sensitivity(39,40), which has  
317 been used in several studies(41–45). In order to identify only primary pancreatic  
318 cancers, but not pancreatic metastases or secondary pancreatic cancers, we excluded  
319 patients with a history of all causes cancers before the index date, which accounted for  
320 about one third of cases. Nevertheless, one fifth of diagnoses that led to these  
321 exclusions were suggestive of misclassified pancreatic cancers (namely ICD-10 codes  
322 D01: Carcinoma in situ of other and unspecified digestive organs; D37: Neoplasm of  
323 uncertain or unknown behavior of oral cavity and digestive organs; C24: Malignant

324 neoplasm of other and unspecified parts of biliary tract), half of them identified in the 2  
325 months preceding the index date. Consequently, our selection procedure was very  
326 conservative. However, there is no reason to believe that this could have biased the  
327 results or prevented their generalization. Moreover, we found that about 9 out of 10 of all  
328 pancreatic cancers were adenocarcinoma, most often localized in the head of the  
329 pancreas, which is consistent with the epidemiology of the disease(21,23). Third, many  
330 covariates were available in the SNDS, and could have been taken into account in the  
331 analyses. Among them, smoking is a major risk factor for pancreatic cancer. In this  
332 study, prevalence of tobacco use was consistent with the figures of daily smoking  
333 reported within the same age groups in a national survey(46). Moreover, the magnitude  
334 of the association with pancreatic cancer was comparable to those of a meta-analysis of  
335 82 studies(47). Fourth, PPI exposure could have been measured during a period of up  
336 to 13 years (2006-2018), in a time frame compatible with the development of pancreatic  
337 cancer. Finally, the careful implementation of the study design, and numerous sensitivity  
338 analyses contributed to the robustness of our results. The case-control and the cohort  
339 design are two observational designs relevant for studying drug-cancer associations,  
340 with similar underlying concepts(48). Here, a cumulative dose-response investigation  
341 was needed for establishing plausibility of a causal effect. Thus the case-control  
342 approach was privileged to compute the exposure level of cases and controls. The  
343 results were consistent across several sensitivity analyses. Notably, an increased risk of  
344 pancreatic cancer was also observed with PPI compared to H2RA use, suggesting that  
345 confounding by indication was likely to be limited.

346 Our study also has some limitations. Given its observational nature, it is prone to  
347 bias(48,49), including residual confounding, time-related bias, and misclassification of  
348 exposure. Residual confounding may have occurred, first, because information on  
349 genetic, family history, lifestyle, and environmental risk factors for cancers was not  
350 available. Analyses, though, were adjusted for other identifiable potential risk factors of  
351 pancreatic cancers, including diabetes mellitus, tobacco, and morbid obesity. Second,  
352 the indication for PPI treatment was not recorded in the databases, and thus could not  
353 be taken into account in the analyses. Third, the lack of an active comparator in the main  
354 analyses may also have led to residual confounding(34). The results of the sensitivity  
355 analysis considering H2RAs as an active comparator must be interpreted cautiously,  
356 since H2RA use is restricted to a small number of users with specific profiles in  
357 France(50). However, they support the finding of an excess risk of pancreatic cancer  
358 development associated with PPI exposure as compared to H2RAs. Time-related biases  
359 were limited by design. Exclusion of cases and controls with an observation period  
360 under 7 years resulted in similar duration of exposure opportunity time, minimizing time-  
361 window bias. Nevertheless, even studies with similar observation periods between cases  
362 and controls can in some instances, introduce differential drug-treated time-window,  
363 when the duration of treated disease is different(49). Here, information on the nature,  
364 and onset date of the condition that led to the initiation of PPI therapy was not available.  
365 Thus, time window bias cannot be fully ruled out. However, given the careful selection of  
366 controls and their matched index dates, such a bias is likely to be limited if any. We  
367 employed a very conservative method to address latency time bias and reverse  
368 causality (or protopathic bias)(30), excluding new PPI users in 2 years before the index  
369 date in the main analysis, and applying 2-year and 4-year lag-times in sensitivity

370 analyses. The lagged analyses tended to decrease the magnitude of the associations  
371 with the highest cDDD categories. This may either suggest potential residual reverse  
372 causality, or reflect excessive caution in the choice of the delay. Using very long lag  
373 periods could tend to unjustifiably consider lower level of exposures, which translates to  
374 lower ORs in the case of a dose-response association(51). Finally, potential  
375 misclassification of exposure status may have occurred. Cumulative exposure to PPIs  
376 was estimated based on the quantity redeemed, but there is no guarantee on patient's  
377 adherence to the prescription, or even that the patient actually took the drug. This bias is  
378 not expected to affect long-term users, with regularly redeemed prescription. Otherwise,  
379 the SNDS does not contain information neither on inpatient nor on OTC PPI use.  
380 However, these uses are quantitatively much lower than outpatient use. Moreover, in  
381 this study, rates of inpatient or OTC PPI uses were not supposed to be different between  
382 cases and controls nor to introduce differential bias.

### 383 **Conclusion**

384 Based on these findings, a slight increase in the risk of pancreatic cancers associated  
385 with the use of PPIs at high cumulative doses cannot be excluded. Given the massive  
386 PPI use, even a relatively modest association would have important public health  
387 implications. Therefore, efforts should be continued to limit PPI treatments to appropriate  
388 indications and durations. Regular monitoring and re-evaluation of treatment are  
389 needed.

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## TABLES

**Table 1. Baseline Characteristics of Pancreatic Cancer Cases and Controls**

	<b>Cases N=23,321</b>	<b>Controls N=75,937</b>
<b>Sociodemographic characteristics</b>		
Age <sup>a</sup> (years), mean (SD)	69.8±10.1	70.0±10.0
40-64 years, n (%)	6694 (28.7)	21,188 (27.9)
≥65 years, n (%)	16,627 (71.3)	54,749 (72.1)
Men <sup>a</sup> , n (%)	12,061 (51.7)	39,370 (51.8)
CMUC <sup>b</sup> , n (%)	765 (11.4)	1669 (7.9)
Social deprivation index (quintiles), n (%)		
1 (least deprivation)	4209 (18.0)	13,997 (18.4)
2	4136 (17.7)	13,896 (18.3)
3	4524 (19.4)	15,007 (19.8)
4	4740 (20.3)	15,506 (20.4)
5 (highest deprivation)	4963 (21.3)	15,083 (19.9)
Missing	749 (3.2)	2448 (3.2)
<b>Comorbidities, n (%)</b>		
Diabetes mellitus	7177 (30.8)	13,304 (17.5)
Complications of diabetes mellitus	882 (3.8)	1597 (2.1)
Tobacco-related diseases or drug use	3544 (15.2)	7673 (10.1)
Morbid obesity	2936 (12.6)	7531 (9.9)
Alcohol-related diseases or drug use	1691 (7.3)	2711 (3.6)
Acute pancreatitis	825 (3.5)	439 (0.6)
Chronic pancreatitis	474 (2.0)	155 (0.2)
Pancreatic cyst	825 (3.5)	156 (0.2)
Gallstones	1425 (6.1)	2655 (3.5)
Hepatitis B or C	211 (0.9)	454 (0.6)
Gastroesophageal reflux disease	3290 (14.1)	8459 (11.1)
Peptic ulcer	455 (2.0)	1026 (1.4)
<i>Helicobacter pylori</i> eradication	910 (3.9)	2407 (3.2)
Myocardial infarction	1084 (4.6)	3129 (4.1)
Congestive heart failure	2051 (8.8)	5609 (7.4)
Peripheral vascular disease	2006 (8.6)	4595 (6.1)
Cerebrovascular disease	1788 (7.7)	5118 (6.7)
Dementia	1555 (6.7)	5300 (7.0)
Chronic obstructive pulmonary disease	5325 (22.8)	14,869 (19.6)
Connective Tissue Disease	449 (1.9)	1316 (1.7)
Mild liver disease	895 (3.8)	1521 (2.0)
Hemiplegia	588 (2.5)	1733 (2.3)
Moderate to severe chronic kidney disease	922 (4.0)	2400 (3.2)
Moderate to severe liver disease	259 (1.1)	347 (0.5)
AIDS	63 (0.3)	148 (0.2)
<b>Comedications<sup>c</sup>, n (%)</b>		
Antihypertensive drugs	14,547 (62.4)	43,658 (57.5)
Nonsteroidal anti-inflammatory drugs	17,579 (75.4)	55,441 (73.0)
Statins	9527 (40.9)	28,514 (37.5)

SD, standard deviation; CMUC, complementary universal health insurance.

<sup>a</sup>Matching variables.

<sup>b</sup>Among individuals aged under 65 years only.

<sup>c</sup>At least 3 redeemed prescriptions within 8 years prior to index date.

**Table 2. Characteristics of Pancreatic Cancer Cases at the Time of Diagnosis**

	<b>Cases N=23,321</b>
<b>Age (years), mean (SD)</b>	69.8±10.1
<b>Men, n (%)</b>	12,061 (51.7)
<b>Year of diagnosis, n (%)</b>	
2014	3975 (17.0)
2015	4416 (18.9)
2016	4878 (20.9)
2017	4922 (21.1)
2018	5130 (22.0)
<b>Cancer localization, n (%)</b>	
Head of pancreas	12,438 (53.3)
Body of pancreas	3222 (13.8)
Tail of pancreas	3025 (13.0)
Pancreatic duct	461 (2.0)
Neck of pancreas	769 (3.3)
Unspecified	3406 (14.6)
<b>Region of residence, n (%)</b>	
Île-de-France	3577 (15.3)
Centre-Val de Loire	1012 (4.3)
Bourgogne-Franche-Comté	1135 (4.9)
Normandie	1217 (5.2)
Hauts-de-France	2023 (8.7)
Grand Est	1884 (8.1)
Pays de la Loire	1255 (5.4)
Bretagne	1007 (4.3)
Nouvelle-Aquitaine	2262 (9.7)
Occitanie	2225 (9.5)
Auvergne-Rhône-Alpes	3051 (13.1)
Provence-Alpes-Côte d'Azur	2099 (9.0)
Corse	122 (0.5)
Oversea territories	452 (1.9)

SD, standard deviation.

**Table 3. Association Between Exposure to Proton Pump Inhibitors and Pancreatic Cancer**

<b>Exposure to Proton Pump Inhibitors</b>	<b>Cases N=23,321</b>	<b>Controls N=75,937</b>	<b>Crude Odds Ratio (95% CI)</b>	<b>Adjusted Odds Ratio<sup>a</sup> (95% CI)</b>	<b>Adjusted Odds Ratio<sup>b</sup> (95% CI)</b>
<b>Ever use, n (%)</b>					
No	5180 (22.2)	18,630 (24.5)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	18,141 (77.8)	57,307 (75.5)	1.15 (1.10-1.19)	1.10 (1.05-1.14)	1.05 (1.01-1.09)
<b>Cumulative defined daily dose (cDDD), n (%)</b>					
0 cDDD	5180 (22.2)	18,630 (24.5)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1-30 cDDD	3186 (13.7)	12,500 (16.5)	0.92 (0.88-0.97)	0.92 (0.88-0.97)	0.92 (0.87-0.97)
31-180 cDDD	4720 (20.2)	16,056 (21.1)	1.08 (1.03-1.13)	1.07 (1.02-1.12)	1.05 (1.00-1.11)
181-1080 cDDD	5087 (21.8)	14,578 (19.2)	1.31 (1.25-1.38)	1.23 (1.17-1.29)	1.18 (1.12-1.24)
>1080 cDDD	5148 (22.1)	14,173 (18.7)	1.40 (1.34-1.47)	1.24 (1.17-1.30)	1.17 (1.10-1.23)
<b>By PPI subtype (ever use), n (%)</b>					
<b>Omeprazole</b>					
No	11,464 (49.2)	39,548 (52.1)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	11,857 (50.8)	36,389 (47.9)	1.13 (1.09-1.16)	1.11 (1.08-1.15)	1.08 (1.04-1.12)
<b>Esomeprazole</b>					
No	12,599 (54.0)	45,118 (59.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	10,722 (46.0)	30,819 (40.6)	1.28 (1.24-1.32)	1.22 (1.18-1.26)	1.18 (1.14-1.22)
<b>Lansoprazole</b>					
No	17,035 (73.0)	56,822 (74.8)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	6286 (27.0)	19,115 (25.2)	1.10 (1.06-1.13)	1.08 (1.05-1.12)	1.05 (1.01-1.09)
<b>Pantoprazole</b>					
No	14,654 (62.8)	50,341 (66.3)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	8667 (37.2)	25,596 (33.7)	1.17 (1.14-1.21)	1.14 (1.10-1.17)	1.09 (1.06-1.13)
<b>Rabeprazole</b>					
No	18,930 (81.2)	62,615 (82.5)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Yes	4391 (18.8)	13,322 (17.5)	1.09 (1.05-1.14)	1.07 (1.03-1.12)	1.03 (0.99-1.08)

CI, confidence interval.

<sup>a</sup>Adjusted for history of diabetes mellitus, tobacco-related diseases or drug use, morbid obesity, alcohol-related diseases or drug use, acute pancreatitis, chronic pancreatitis, pancreatic cyst, gallstones, hepatitis B or C.

<sup>b</sup>Final model adjusted for deprivation index, history of diabetes mellitus, tobacco-related diseases or drug use, morbid obesity, alcohol-related diseases or drug use, acute pancreatitis, chronic pancreatitis, pancreatic cyst, gallstones, hepatitis B or C, gastroesophageal reflux disease, peptic ulcer, *Helicobacter pylori* eradication, peripheral vascular disease, dementia, mild liver disease, AIDS, use of anti-hypertensive drugs, nonsteroidal anti-inflammatory drugs, and statin use.

**Table 4. Association Between Ever Use of Proton Pump Inhibitors and Pancreatic Cancer, Separately by Patient Characteristics**

	Cases N=23,321	Controls N=75,937	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio <sup>b</sup> (95% CI)
	Exposed/Total	Exposed/Total		
<b>Age<sup>a</sup>, n (%)</b>				
40-64 years	4971/6694 (74.3)	14,963/21,188 (70.6)	1.21 (1.13-1.29)	1.05 (0.97-1.13)
65-85 years	13,170/16,627 (79.2)	42,344/54,749 (77.3)	1.11 (1.07-1.17)	1.04 (0.99-1.10)
<b>Sex<sup>a</sup>, n (%)</b>				
Male	9039/12,061 (74.9)	28,597/39,370 (72.6)	1.13 (1.07-1.19)	1.02 (0.97-1.08)
Female	9102/11,260 (80.8)	28,710/36,567 (78.5)	1.17 (1.11-1.24)	1.08 (1.02-1.15)
<b>Calendar year<sup>a</sup>, n (%)</b>				
2014	2918/3975 (73.4)	9128/12,897 (70.8)	1.15 (1.05-1.25)	1.05 (0.96-1.16)
2015	3347/4416 (75.8)	10,560/14,261 (74.0)	1.10 (1.01-1.19)	0.97 (0.88-1.06)
2016	3815/4878 (78.2)	11,860/15,821 (75.0)	1.21 (1.12-1.32)	1.14 (1.04-1.25)
2017	3927/4922 (79.8)	12,437/16,083 (77.3)	1.17 (1.08-1.27)	1.09 (1.00-1.20)
2018	4134/5130 (80.6)	13,322/16,875 (78.9)	1.11 (1.02-1.21)	1.00 (0.91-1.09)
<b>Cancer localization, n (%)</b>				
Head of the pancreas	9603/12,438 (77.2)	30,455/40,610 (75.0)	1.14 (1.08-1.20)	1.04 (0.98-1.10)
Other	8538/10,883 (78.5)	26,852/35,327 (76.0)	1.16 (1.10-1.22)	1.06 (1.00-1.13)
<b>History of diabetes mellitus<sup>c</sup>, n (%)</b>				
No	12,270/16,144 (76.0)	46,487/62,633 (74.2)	1.14 (1.10-1.19) <sup>c</sup>	1.07 (1.02-1.12) <sup>c</sup>
Yes	5,871/7177 (81.8)	10,820/13,304 (81.3)	1.06 (0.98-1.15) <sup>c</sup>	0.99 (0.91-1.07) <sup>c</sup>
<b>History of tobacco-related diseases or drug use<sup>c</sup>, n (%)</b>				
No	15,058/19,777 (76.1)	50,701/68,264 (74.3)	1.14 (1.09-1.18) <sup>c</sup>	1.05 (1.01-1.10) <sup>c</sup>
Yes	3083/3544 (87.0)	6606/7673 (86.1)	1.12 (0.99-1.26) <sup>c</sup>	1.02 (0.90-1.16) <sup>c</sup>
<b>Morbid obesity<sup>c</sup>, n (%)</b>				
No	15,503/20,385 (76.1)	50,602/68,406 (74.0)	1.14 (1.10-1.19) <sup>c</sup>	1.05 (1.01-1.10) <sup>c</sup>
Yes	2638/2936 (89.9)	6705/7531 (89.0)	1.12 (0.98-1.29) <sup>c</sup>	1.00 (0.86-1.17) <sup>c</sup>

CI, confidence interval.

<sup>a</sup>Matching variables.

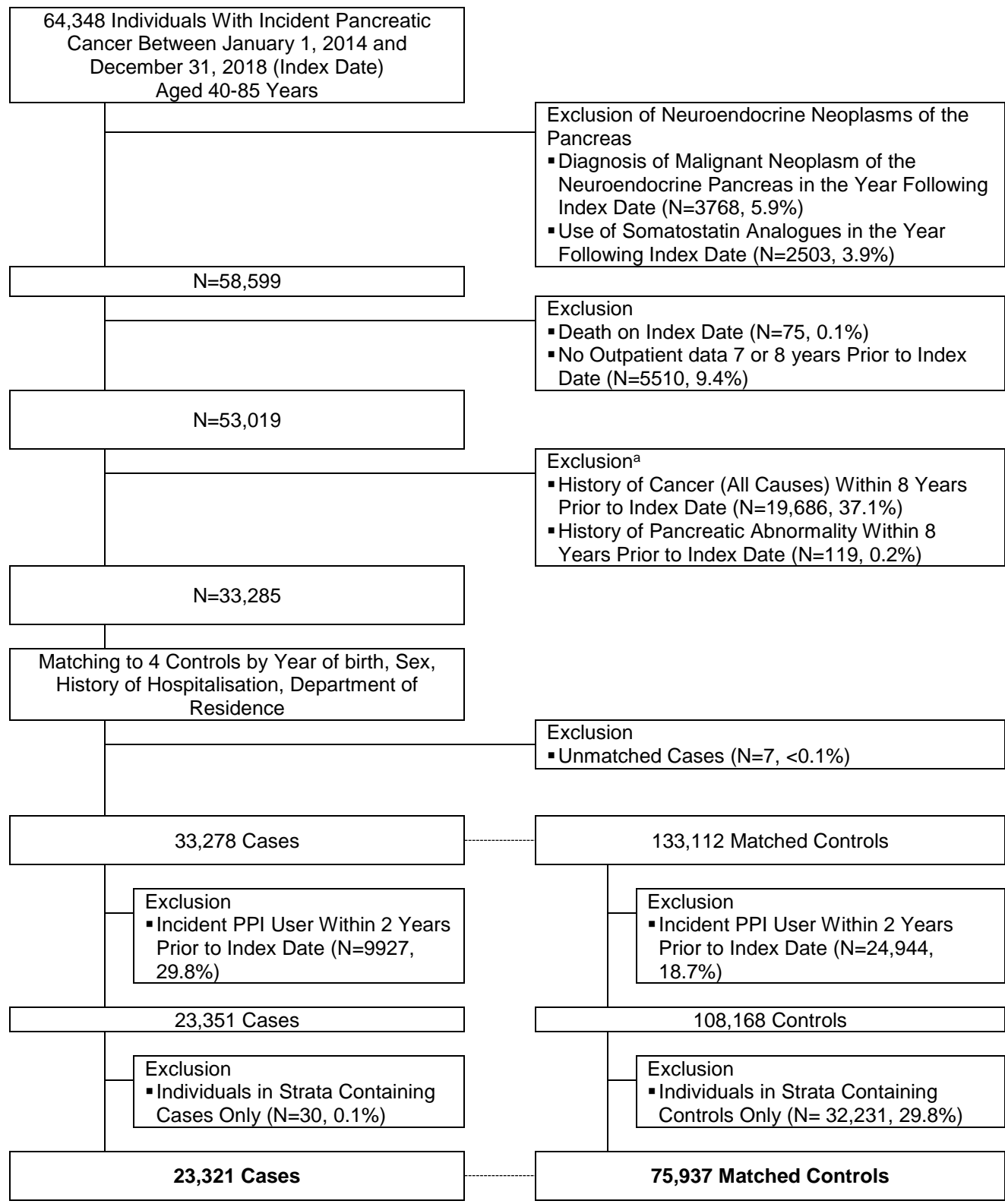
<sup>b</sup>Final model adjusted for deprivation index, history of diabetes mellitus, tobacco-related diseases or drug use, morbid obesity, alcohol-related diseases or drug use, acute pancreatitis, chronic pancreatitis, pancreatic cyst, gallstones, hepatitis B or C, gastroesophageal reflux disease, peptic ulcer, *Helicobacter pylori* eradication, peripheral vascular disease, dementia, mild liver disease, AIDS, use of anti-hypertensive drugs, nonsteroidal anti-inflammatory drugs, and statin use.

<sup>c</sup>The risk factor of pancreatic cancer was introduced in the model along with an interaction term with PPI use. The p value for interaction was of 0.08 for history of diabetes mellitus, 0.67 for history of tobacco-related diseases or drug use, and 0.55 for morbid obesity.

## **FIGURE LEGENDS**

Figure 1. Study Flow Chart

Figure 1 shows the flowchart of the study, and the number of patients included in the case and in the control groups.



PPI, proton pump inhibitor.

<sup>a</sup>Codes available in Supplementary Table S1.

**Figure 1**

# Cancer Epidemiology, Biomarkers & Prevention

## Use of Proton Pump Inhibitors and Risk of Pancreatic Cancer: A Nationwide Case-Control Study Based on the French National Health Data System (SNDS)

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